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EFFECTS OF ^{60}Co ON ELECTRICAL SELF-STIMULATION OF THE BRAIN AND BLOOD PRESSURE

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The effects of 1000 and 2000 rad ^{60}Co on electrical self-stimulation of subcortical brain areas and blood pressure were investigated to determine whether radiation-induced performance decrement occurs in a like manner for a positively-rewarded behavioral task as it does for the more typically studied shock-avoidance task. During the early postradiation minutes self-stimulation responses decreased or ceased and resumed shortly

20. ABSTRACT (Continued)

thereafter, revealing a similar course of performance decrement as seen with shock-avoidance, discrimination tasks. Early postradiation hypotension with subsequent recovery paralleled the performance decrement, reproducing the blood pressure-behavior correlations seen previously with shock reinforcement. The blood pressure elevating influence of the brain stimulation observed prior to irradiation was diminished or absent during the deep hypotensive stage postradiation, but tended to return minutes later.

PREFACE

Monkeys undergo a transient period of performance decrement and hypotension minutes after exposure to high-dose (e.g., ~1000 rad), high-dose rate (e.g., >150 rad/min) ionizing radiation. Performance decrement has been assessed heretofore only with behavioral tasks motivated, in a negative fashion, by shock-avoidance reinforcement. The objective of the present study was to determine whether radiation-induced performance decrement occurs in a like manner for a positively rewarded behavioral task as it does for the more typically studied shock-avoidance task. The measure presently employed was rate of responding for positively reinforcing electrical self-stimulation of the brain via implanted electrodes.

It was found that self-stimulation responding diminished or ceased within minutes of irradiation, but tended to recover to a normal level several minutes later. In a parallel time frame, the animals underwent a phasic hypotensive episode with subsequent recovery. These changes correspond directly with the behavior-blood pressure alterations seen in previous studies using shock-avoidance techniques. It was concluded that the aversive motivational properties of shock reinforcement are not necessary for the

postradiation performance decrement phenomenon.

It was also found that the blood pressure elevating influence of the present brain stimulation observed prior to irradiation was diminished or absent during the deep hypotensive stage postradiation, but tended to return minutes later, in the same phasic time frame as for performance and blood pressure. The latter observation correlates with other recent demonstrations of early, transitory depression of the CNS following irradiations in the present dose range.

The author gratefully acknowledges the assistance of Mr. W. Hicks, Dr. E. A. Henderson, and Mr. R. A. Hutton.

This research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences, National Research Council.

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INTRODUCTION

Within a few minutes of exposure to a sufficiently high-dose of whole-body, ionizing radiation, primates undergo a transient period of moderate to severe hypotension, which is frequently accompanied by performance decrement or incapacitation.[11,13] The animal revives promptly following this period and resumes a normal performance level.[2] The etiology of this phenomenon is not well understood.

Attempts thus far to relate the physiological and behavioral effects of irradiation in monkeys have utilized as performance measures tasks based on shock-avoidance almost exclusively. Positively motivated tasks have not been employed as they customarily utilize food reward, and irradiation characteristically evokes emesis and anorexia, which by themselves would obviously deter food-seeking behaviors. Of interest in the present study was whether a positively motivated performance task, not dependent on appetitive reinforcement, would be affected by irradiation in a manner similar to that seen with shock-avoidance tasks.

The present efforts involved testing the effects of irradiation on rate of responding for positively reinforcing electrical stimulation of the brain (self-stimulation).

Of considerable additional interest was the fact that arterial blood pressure was, in most cases, increased by the brain stimulation used. Therefore, the stimulation's efficacy in offsetting radiation-induced hypotension could be examined.

The only previous studies of radiation effects on self-stimulation utilized rats exposed to much lower dose rates (e.g., 20 rad/min) than of relevance here.[4,5] When measured over days following 600-rad X-irradiation, the initially high-response rate rats showed faster responding postradiation, while initially slow rats slowed further.

METHODS AND MATERIALS

Ten rhesus monkeys (Macaca mulatta) were chronically implanted stereotaxically[8] with six concentric, bipolar stainless steel electrodes* aimed at various subcortical targets. After at least two weeks post-operative recovery, each electrode point was tested for stimulation effects. The constant current brain stimulus consisted of a one-half second train of 100 Hz, biphasic rectangular pulse pairs,

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* Rhodes Medical Instr., Model NEX-100, 21044 Ventura Blvd., Woodland Hills, California 91364.

each pulse 1 msec in duration, with no delay between positive and negative phases.

Each animal was tested in a restraining chair facing a panel containing a rod-shaped lever, 3/8 in. in diameter, protruding 3 in. from the panel, depression of which triggered the brain stimulus. Current thresholds were determined for movement or emotional reactions, and several 1-hr test sessions were devoted to attempting to shape lever pressing, trying each electrode which appeared to mediate excitement, orienting, chewing, or sniffing. The currents used ranged from 0.3 to 2.5 milliamps.

When self-stimulation was forthcoming from one of the electrode sites, 1-hr daily sessions were run for at least 5 days to stabilize the pressing rate. Otherwise, only manually administered brain stimulation effects were noted. Following this stage, each animal was surgically implanted under halothane with a femoral arterial catheter projecting into the abdominal aorta from which arterial blood pressure (BP) was monitored with a Kulite PSL 125-6 Pressure Transducer† and a polygraph write out. One week

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† Kulite Semiconductor Products, 1039 Hoyt Avenue, Ridgefield, New Jersey 07657.

postoperatively the animal was run for several more days on self-stimulation to restabilize lever pressing prior to irradiation.

The animals were then monitored before, during, and after 1000 or 2000 rad, mid-body absorbed dose of ^{60}Co gamma at the Air Force Weapons Laboratory Large Animal Irradiation Facility located on Kirtland Air Force Base, Albuquerque, New Mexico. Each animal sat in its regular restraining chair and worked at the self-stimulation task, providing it was a self-stimulator, while oriented with its back toward the ^{60}Co source. The mid-body dose rate was between 183 and 193 rad/min. Further details of the exposure parameters and dosimetry are available in Bruner.[2]

Following the experiment, the animals were sacrificed and the brains perfused and stored using 10 percent formalin. The brains were later removed and sectioned on a freezing microtome allowing visual localization of the electrode tracks and tips which were photographed.

RESULTS

Self-Stimulation Performance Effects

Consistent self-stimulation behavior was observed in five monkeys prior to irradiation, with the response

rates ranging from over 50 down to about 5 presses per minute (Figs. 1-5). Two monkeys frequently self-stimulated at high rates but occasionally paused for one or more minutes (Figs. 6 and 7), which the consistent animals mentioned first did not do during pretesting. The three remaining animals did not self-stimulate and so were tested only for the effects on BP of manually administered stimulation (Figs. 8-10).

The five consistent self-stimulators all slowed or stopped lever pressing at some time beginning after 3 min following the start of irradiation and lasting up to 30 min or more (Figs. 1-5). This is the same period of radiation-induced performance decrement or incapacitation as for shock-avoidance performance tests.[2]

Monkey No. 686 (Fig. 1) showed only a gradual decrease in response rate over the first 15 min postradiation, slowing from about 55/min to around 36/min at the 15th minute where mean BP was only 53 mm Hg. After 20 min postradiation, the animal resumed a response rate averaging 50/min.

Monkey No. 672 (Fig. 2) ceased responding during postradiation minutes 5-15, except for five presses during the 7th minute. By 20 min and thereafter No. 672's response rate had recovered to a moderately high level.

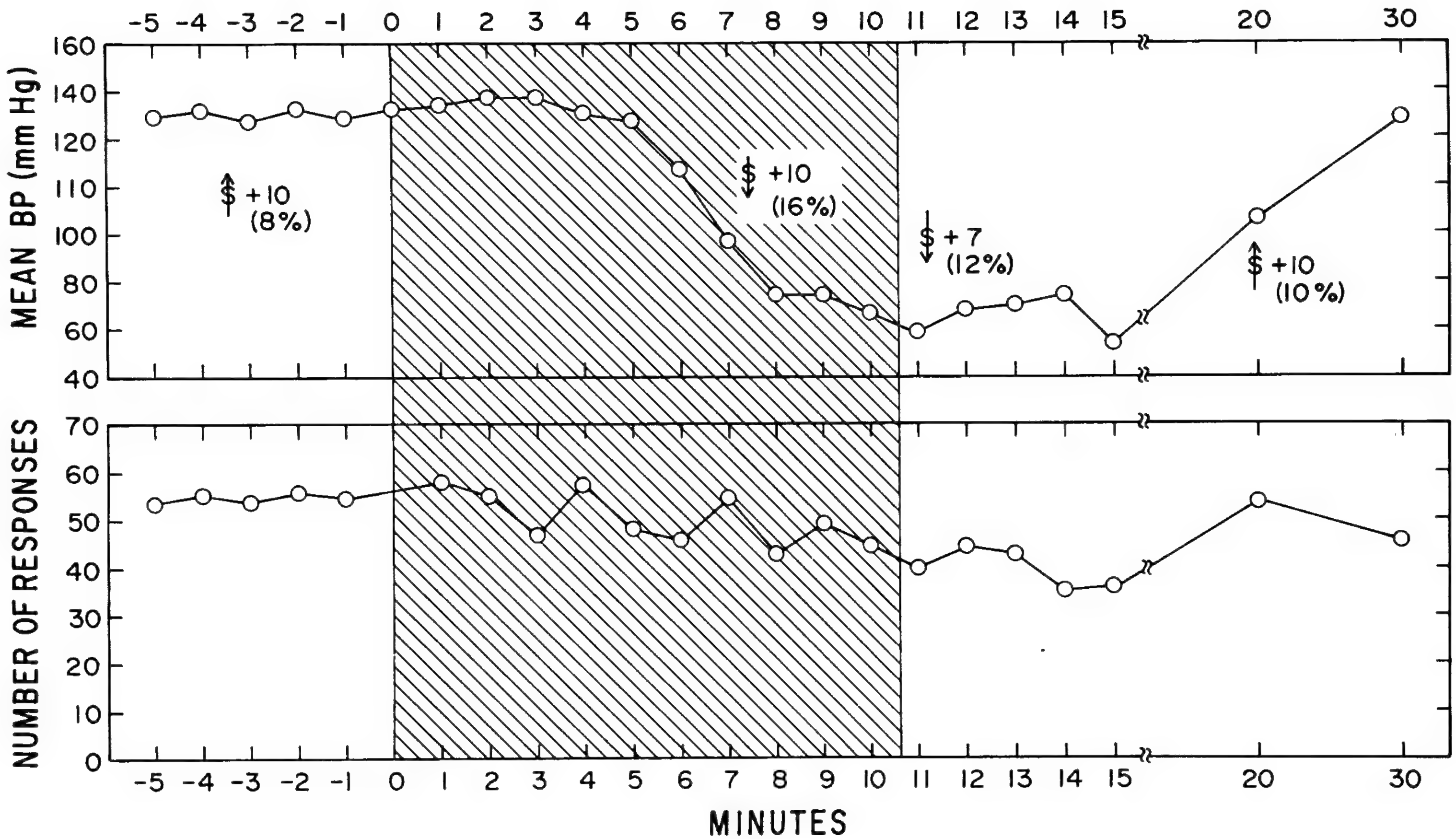


Figure 1. No. 686, 2000 rad. Olfactory Area (A17,L4,H+4). For all figures: Time 0 indicates the start of irradiation period (shaded area). $ indicates selected times of self- or manually-administered stimulation of the brain site identified (with stereotaxic coordinates). The amount of change in blood pressure (in mm Hg) is shown next to the $ symbol, below which is given the percentage change relative to the mean BP existing just before the $.

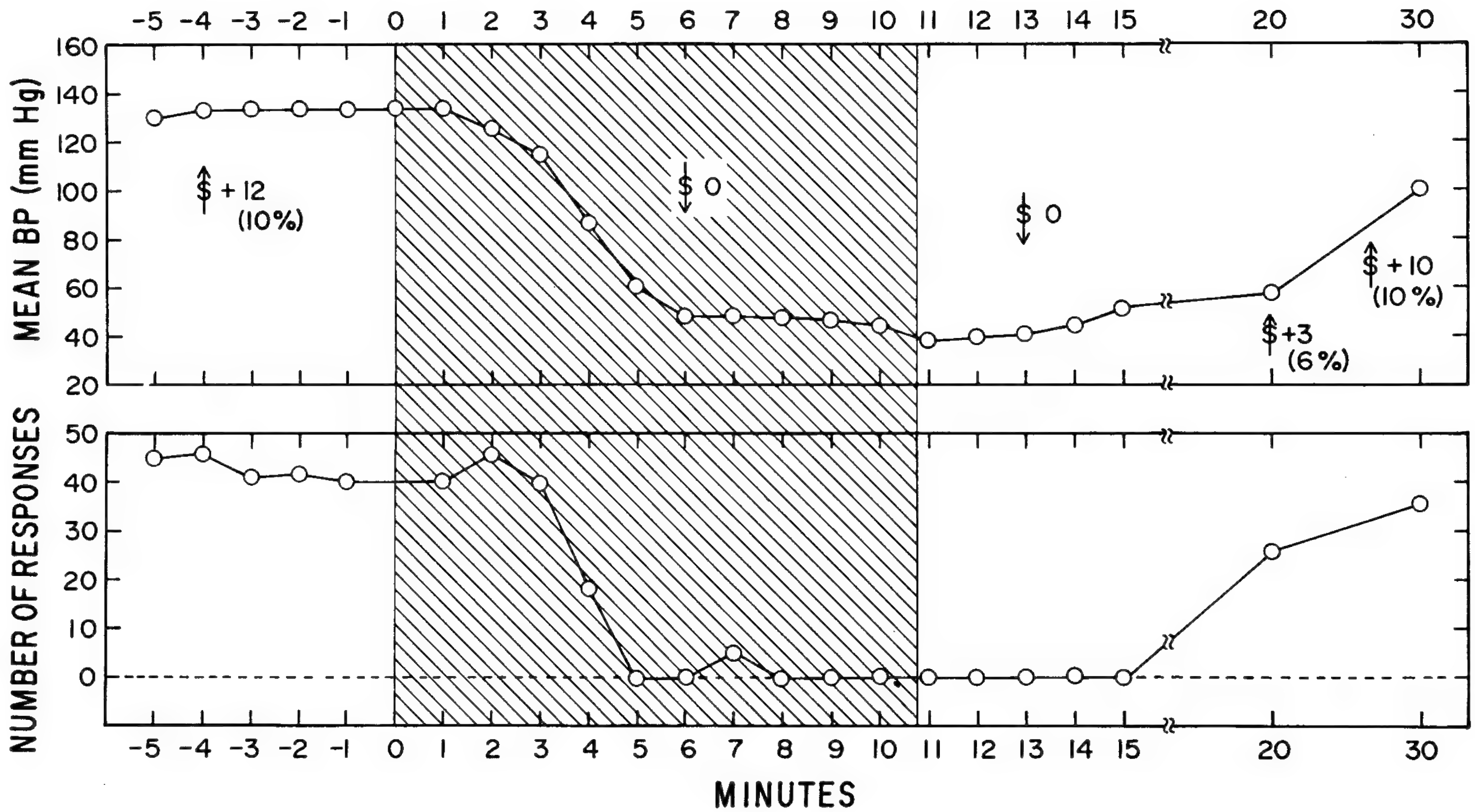


Figure 2. No. 672, 2000 rad. Caudate Nucleus (A17,L4,H+12).

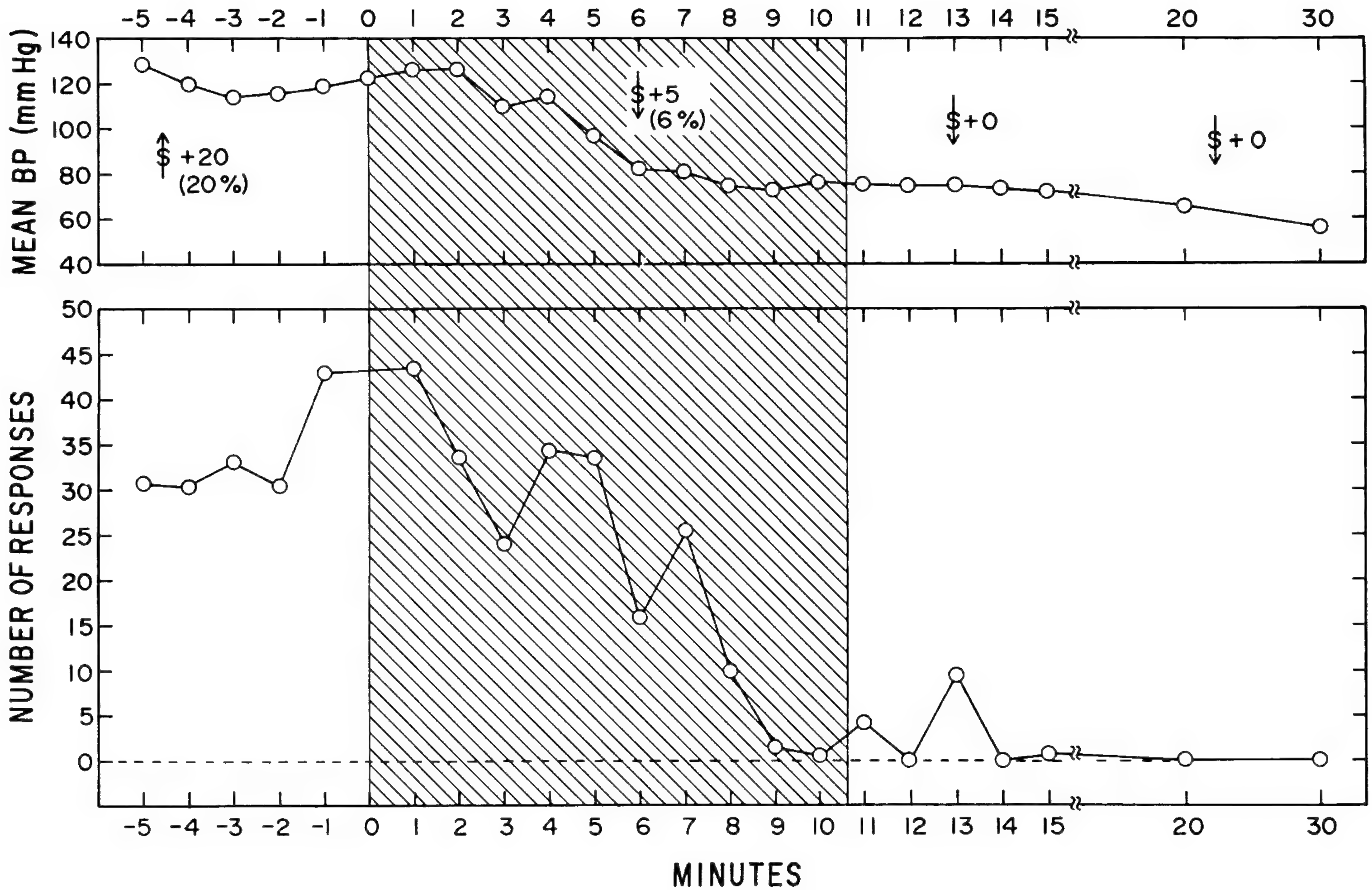


Figure 3. No. 682, 2000 rad. Olfactory Area (A16,L4,H+3).

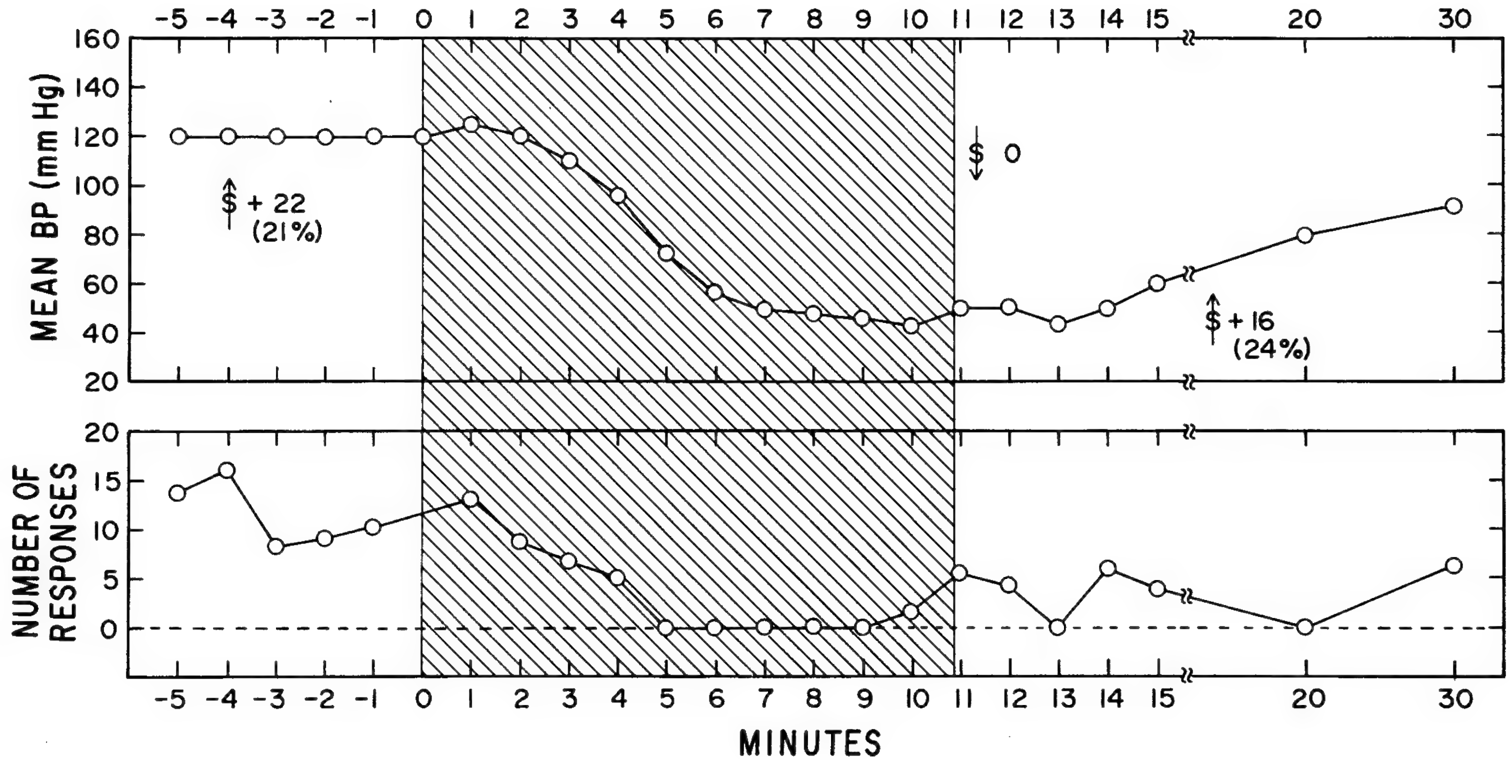
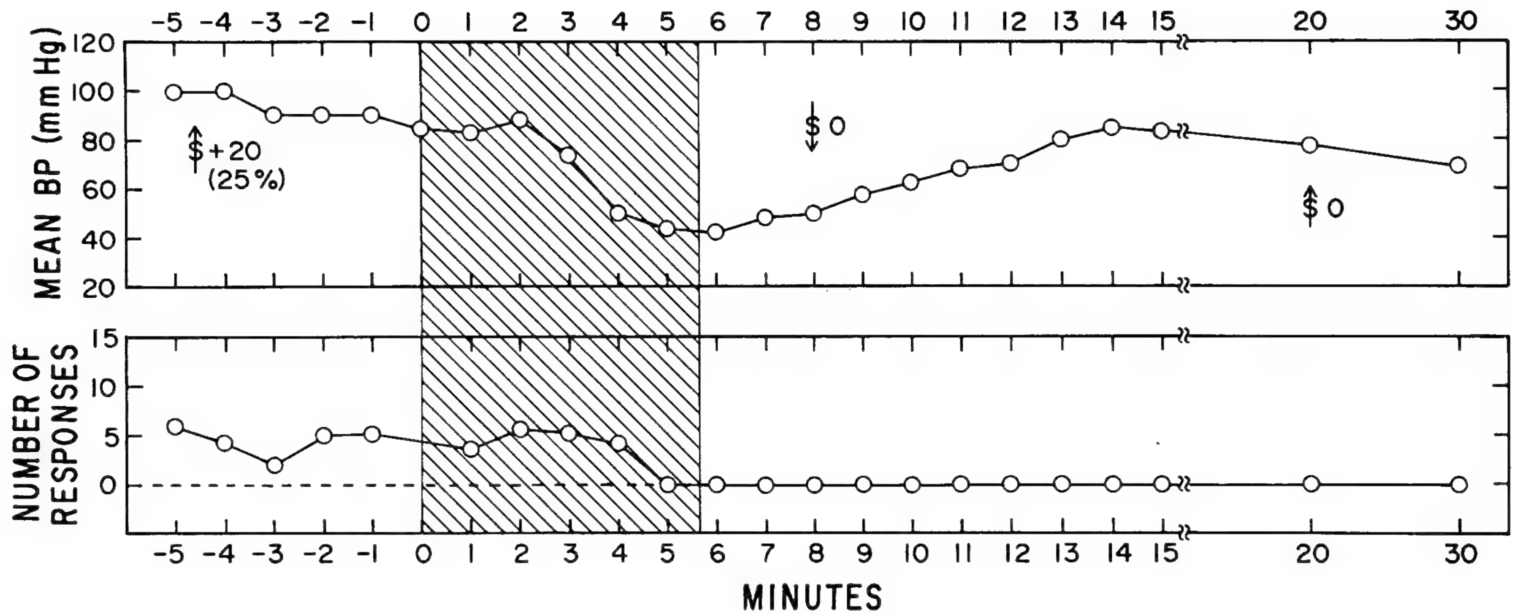


Figure 4. No. 704, 2000 rad. Lateral Hypothalamus (A14½,L3,H+3½).



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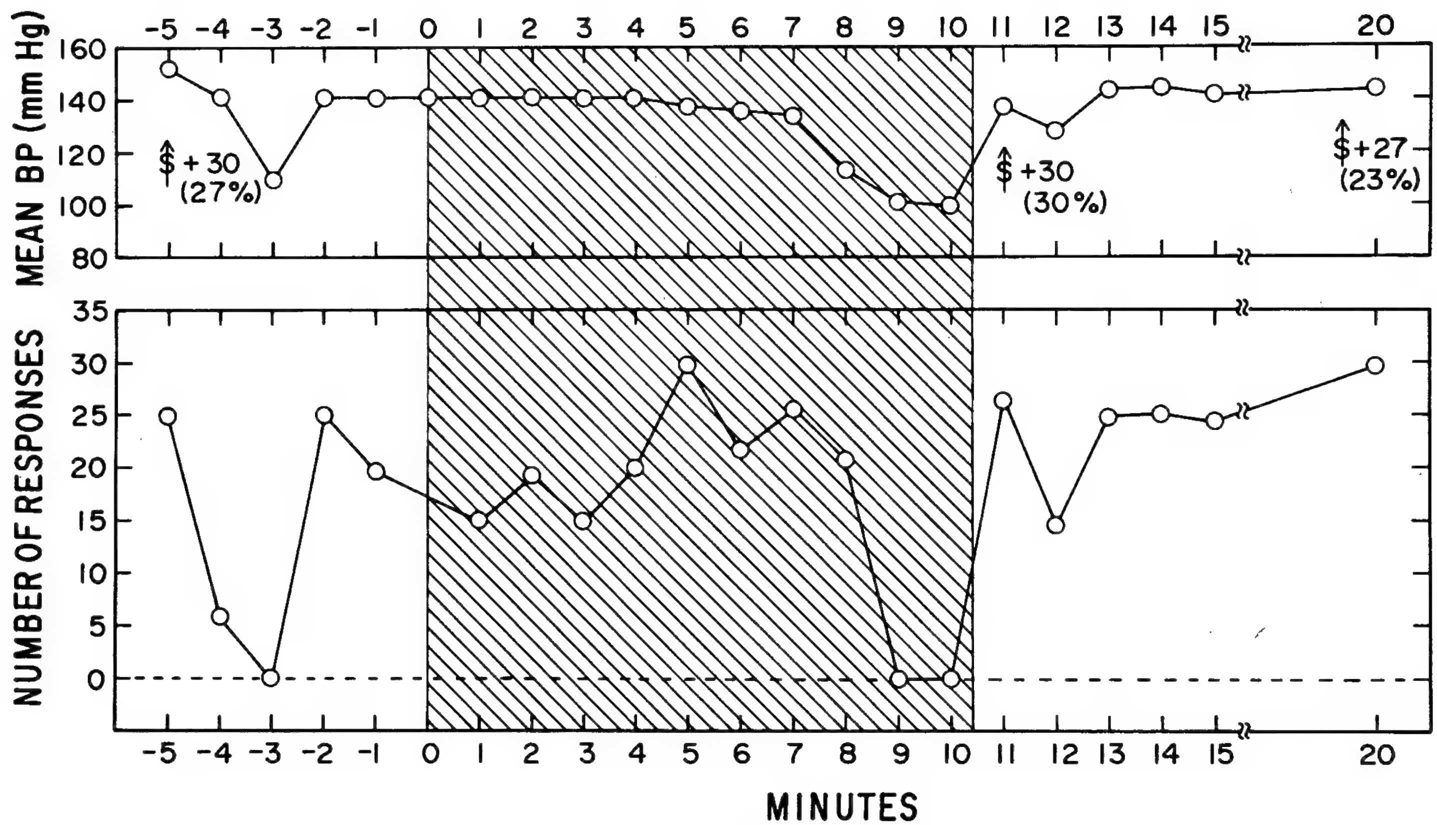


Figure 6. No. 685, 2000 rad. Lateral Hypothalamus (A12,L3,H+2).

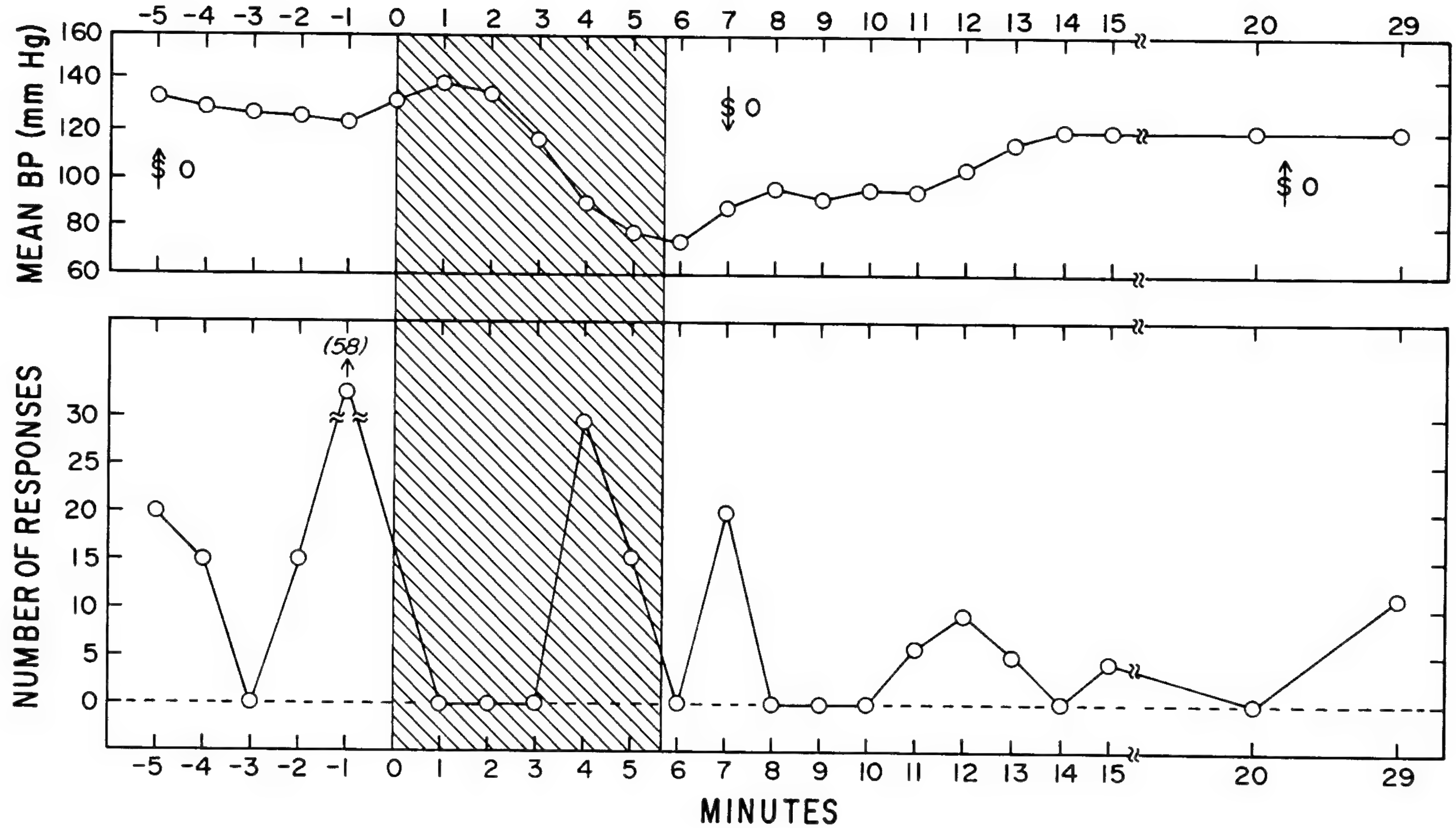
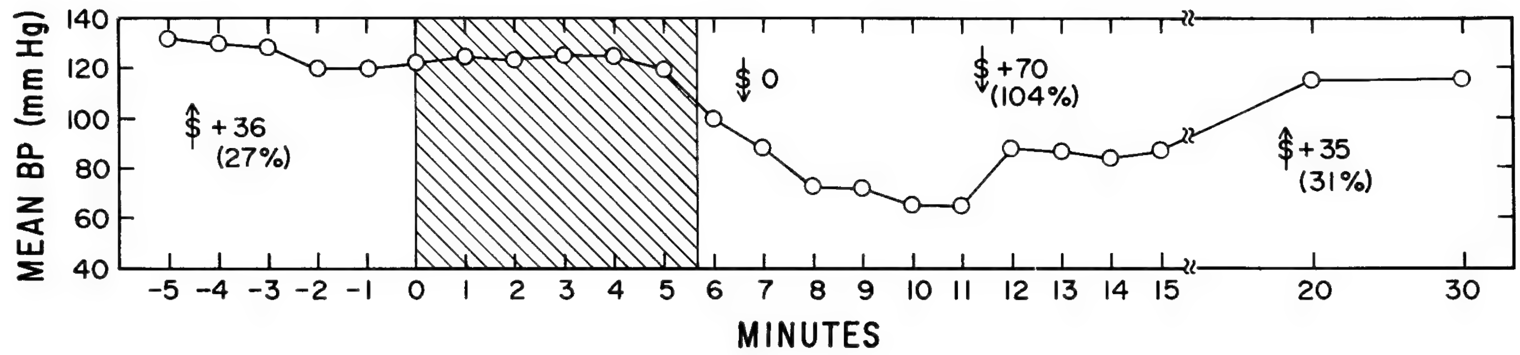


Figure 7. No. 703, 1000 rad. Olfactory Area (A15½, L4, H+2).



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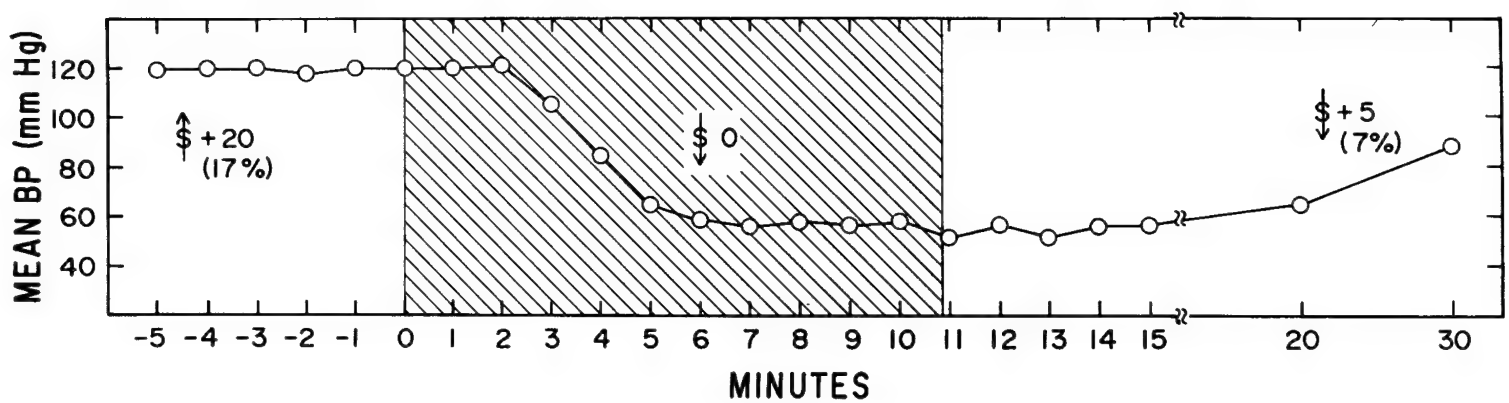

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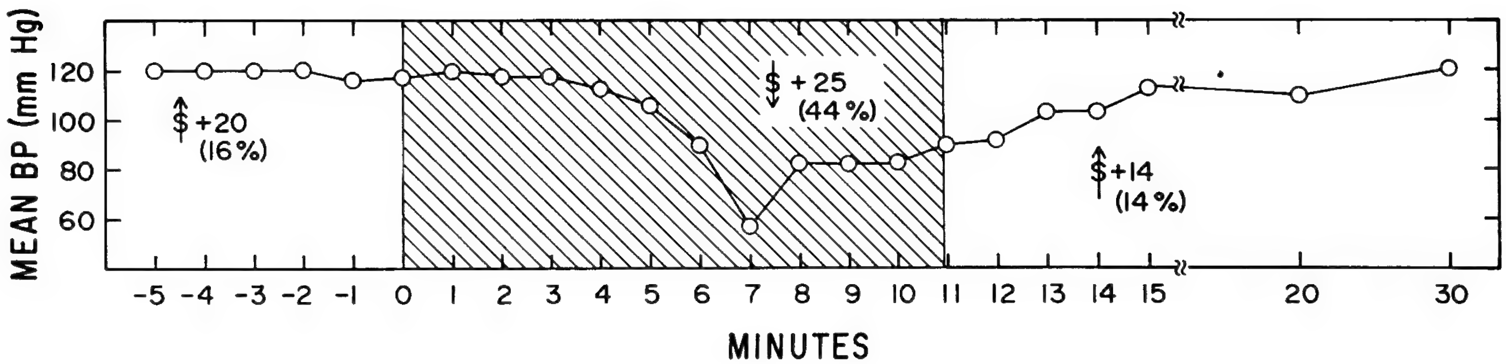

Figure 10. No. 693, 2000 rad. Supraoptic Nucleus (A14½,L4,H+2).

Monkey No. 682 (Fig. 3) stopped pressing during postradiation minutes 5-9, and then resumed pressing erratically. After 30 min, he eventually resumed a normal baseline.

Animals Nos. 704 (Fig. 4) and 711 (Fig. 5) did not show performance recoveries, but rather died after 35 and 90 min, respectively. These two represent the minority of so-called "early deaths" regularly seen in this dose range; most animals receiving up to 2000 rad live several days.

Subjects Nos. 685 (Fig. 6) and 703 (Fig. 7) demonstrated response rates too erratic to permit clear conclusions regarding radition effects. Their data do suggest, however, that No. 685 showed no decrement while No. 703 apparently did so, although such is equivocal.

Blood Pressure Effects

All animals except No. 685 revealed hypotension developing after 3 min following the start of irradiation. Excluding No. 685, the mean BP* decreased 55 percent over

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* Mean BP = $\frac{\text{Systolic BP - Diastolic BP}}{3}$ + Diastolic BP. In the present instance, systolic and diastolic BP exhibited similar trends. Mean BP, therefore, was selected for simplicity in display.

the group measuring at the point of deepest hypotension for each animal relative to its initial BP. As is usual in this radiation-dose range, the BP returned to about 75 percent or more of the preradiation mean value after 30 min, in most cases. The mean time after raising the ^{60}Co source to deepest hypotension was 9.7 min, ranging from 6 to 15 min.

The effects on BP of electrical brain stimulation are indicated in Figures 1-10 before irradiation and at various times afterwards. All but one of the animals (No. 703, Fig. 7) revealed BP increases associated with stimulation of the selected brain site prior to irradiation. Six of the animals showed diminished or absent BP responses to the same stimulation administered during the early postradiation minutes while hypotensive (Figs. 2, 3, 4, 5, 8, and 9; No. 686, Fig. 1, showed a smaller BP response at 11 min in magnitude, but not in percentage). In the ensuing postradiation minutes, when BP had begun to rebound, the stimulation tended to again elicit BP increments (Figs. 2, 3, 8 and 9). Subjects Nos. 704 (Fig. 4) and 711 (Fig. 5), whose BP did not later respond to stimulation, became increasingly moribund and died at 35 and 90 min postradiation, respectively. As noted earlier, these two subjects likewise did not resume lever pressing as did the other self-stimulators.

Monkey No. 685 (Fig. 6) showed no clear developing hypotension postradiation. Two periods of decreased BP are evident, one pre- and one postradiation, both of which are concurrent with periods of no self-stimulation. As the stimulation alone could raise 685's BP by 30 mm Hg, the two low BP periods may have been due to the absence of stimulation rather than due to irradiation.

DISCUSSION

The present findings reveal that the time course and nature of changes in self-stimulation and BP following irradiation are similar to those observed with shock-avoidance tasks.[11,13] This suggests that the aversive motivational properties of shock reinforcement are not necessary for the postradiation performance decrement phenomenon.

The present finding that the BP elevating influence of electrical stimulation of hypothalamic and olfactory area sites is temporarily depressed or abolished during the early postradiation period of hypotension and performance decrement correlates with other recent demonstrations of early, transitory depression of the CNS in the present dose range. MacFarland and Levin observed performance decrement accompanied

by slow wave EEG activity,[6] Willis and MacFarland reported decreased brain temperatures,[12] and Bruner et al. found depressed baroreceptor reflexes,[1] all during the initial 5-15 min following high-dose-rate exposures of like magnitude.

The basis for this transient, generalized CNS depression has still not been elucidated. The often raised question of the postradiation adequacy of the cerebral blood supply and metabolism remains unresolved as a result of contradictory observations,[3,7,10,11] and negative findings.[9] Further research is needed to determine what conditions of deficit must develop rapidly within the nervous system following irradiation in order to make manifest the behavioral and cardiovascular decrements seen.

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